Original Article

FACTORS AFFECTING PROGNOSIS IN PATIENTS WITH COMPLICATED PYELONEPHRITIS

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ABSTRACT

Background: Complicated pyelonephritis, a severe form of urinary tract infection, poses a significant healthcare burden due to its complex management and potential for severe outcomes. Current understanding of its epidemiological and clinical characteristics remains insufficiently detailed. Aim & Objective: This study aims to analyze the epidemiological, clinical, and microbiological characteristics of patients with complicated pyelonephritis, focusing on identifying key factors influencing prognosis in a tertiary care context.

Methods: Conducted at a tertiary care center, this descriptive cross-sectional study enrolled 438 inpatients diagnosed with complicated pyelonephritis. Data on demographic characteristics, clinical presentation, microbiological findings, and patient outcomes were collected and analyzed to discern patterns and correlations.

Results: Among the participants, the distribution was 54.6% male and 45.4% female, with a median age of 48 years. The crude mortality rate observed was 6.89%, with an attributable mortality rate of 4.34%. Escherichia coli was the most common pathogen, identified in 68.65% of cases. Significant bacteremia was present in 34.31% of patients, and antimicrobial resistance was notably prevalent. Diagnostic imaging revealed urological anomalies in 60.86% of patients, underscoring the importance of comprehensive diagnostic evaluations.Conclusion: The findings highlight the critical nature of complicated pyelonephritis and the need for precise diagnostic and management strategies, particularly considering the high prevalence of antimicrobial resistance and the impact of urological anomalies on patient outcomes.

Keywords: Complicated Pyelonephritis, Urinary Tract Infections, Escherichia coli, Antimicrobial

INTRODUCTION:

Persistent renal calculi constitute a significant predisposing factor for urinary tract infections, which, in turn, may escalate into pyelonephritis. This condition potentially leads to a gradual decline in renal function and, in some instances, may culminate in end-stage renal disease.[1] Unaddressed pyelonephritis is at risk of developing into complex conditions such as the critically severe, but rare, emphysematous pyelonephritis (EPN) or the xanthogranulomatous pyelonephritis (XGP).[2] Furthermore, the continuous presence of kidney stones promotes inflammatory and irritative changes within the renal epithelium, facilitating the process of dedifferentiation and dysplasia. Consequently, this process significantly increases the likelihood of oncogenesis in the renal tissue, doubling the risk of cancer development.[3] Despite the abundance of data regarding the epidemiological features and outcomes of uncomplicated acute pyelonephritis[4–6], there is a notable paucity of knowledge concerning the epidemiology, clinical manifestations, microbiological profiles, and prognoses of complicated pyelonephritis.[7] Accurate and swift identification of complex pyelonephritis is crucial due to the increased prevalence of antimicrobial resistance and frequently suboptimal responses to treatment observed when complications are involved, even when utilizing antimicrobials effective against the causative pathogens.[8] Despite the prevailing assumption that hospital admission is necessary for all individuals diagnosed with

complex pyelonephritis, this practice lacks empirical support from rigorous research.[9] The aim of this study is to describe the clinical, epidemiological, and microbiological profiles, as well as the prognosis, of patients with complex pyelonephritis, drawing from a substantial and representative cohort of patients presenting to our hospital with complicated pyelonephritis.

MATERIAL AND METHODS

In this observational study conducted at a single center, a total of 438 inpatients aged 18 and above who were diagnosed with complicated pyelonephritis were enrolled over a specified period at a 1300-bed tertiary care facility. Acute pyelonephritis diagnosis was based on at least two of the following criteria: axillary temperature exceeding 38.6°C, occurrence of chills, flank pain, or presence of tenderness in the costovertebral angle upon palpation, and symptoms consistent with micturition syndrome such as dysuria, frequent urination, suprapubic pain, or urgency. Diagnostic confirmation of pyelonephritis was based on the detection of pyuria, as indicated by a positive leukocyte esterase test on a dipstick, the presence of more than 10 leukocytes per milliliter in uncentrifuged urine or more than 5 leukocytes per high power field (HPF) in centrifuged sediment, or through positive urine culture findings.

The definition of complicated pyelonephritis included cases in patients with male gender, compromised immune systems, or structural or functional anomalies of the urinary tract. This category also comprised individuals with indwelling bladder catheters, nephrostomy tubes, or ureteral stents, those with a single kidney, or patients who had undergone procedures involving the urinary tract within the previous two weeks. The research further outlined the criteria for Systemic Inflammatory Response Syndrome (SIRS) and its escalation to sepsis, severe sepsis, and septic shock. SIRS was recognized by the presence of at least two symptoms among abnormal body temperature (either high or low), accelerated heart rate, increased respiratory rate, or white blood cell count irregularities. The condition of sepsis was identified when the criteria for SIRS were met alongside a clinically or microbiologically confirmed infection. Severe sepsis was distinguished by the occurrence of sepsis accompanied by signs of organ hypoperfusion., and septic shock was defined as sepsis leading to a significant and sustained drop in blood pressure unresponsive to fluid resuscitation. Exclusion criteria included recent significant urological surgery, kidney transplant recipients, or pregnant individuals.

Data collection in this investigation was prospectively conducted following a rigorously designed research protocol. The collected data spanned various variables, including demographic information (such as age and gender), the presence of any underlying nephrourological conditions (including renal stones, non-stone-related ureteral obstructions, bladder anomalies, prostate issues, and recent non-surgical urological procedures), as well as risk factors like a history of urinary tract infections, diabetes, active cancer, and chronic kidney disease. Additional information encompassed clinical symptoms, duration of symptoms, previous antibiotic usage, and outcomes of physical examinations. Laboratory tests conducted at admission included a complete blood count, hemoglobin level, hematocrit, platelet count, C-reactive protein, and serum creatinine levels. Most participants underwent blood and urine analysis immediately upon admission and had an abdominal ultrasound within the first 48 hours. Subsequent diagnostic procedures were determined by the clinical judgment of professionals specializing in emergency, internal, or infectious disease medicine.

For each participant, a 10 mL blood specimen was collected through venipuncture. This sample was subjected to both aerobic and anaerobic bacterial culture tests, with at least two sets of cultures prepared for each individual. The cultures were incubated and monitored using the semiautomatic BACTEC 9240 system for a duration of five days, in alignment with established laboratory practices. Certain bacterial species, specifically Corynebacterium spp., Micrococcus spp., and coagulase-negative staphylococci (Staphylococcus saprophyticus excluded), and Bacillus spp., were deemed contaminants if detected in only one culture set without supportive evidence from urine cultures.

Urine specimens were collected employing either the midstream clean-catch method or direct catheterization. For patients with indwelling catheters, samples were drawn from the catheter's designated sampling port. These urine samples were

then cultured on blood agar and MacConkey agar plates. A culture was considered positive if it yielded one or two types of uropathogens at a concentration of ≥10^4 CFU/mL for noncatheterized patients or ≥10^3 CFU/mL for catheterized patients, accompanied by signs of pyuria. Cultures showing more than two bacterial strains were considered contaminated.

Antimicrobial resistance patterns were assessed using disc diffusion methods and selective media, with discrepancies between urine and blood cultures noted when the latter tested positive for a bacterium absent in the urine culture, showed no bacterial growth, or was deemed contaminated.

In cases of discordant results, the cause of complicated pyelonephritis was attributed to the bacteremiacausing pathogen. Patients were admitted to either a urology ward or intensive care unit based on their clinical presentation, receiving initial broad-spectrum treatment refined upon identifying the causative agent, for a minimum of 10 days. Treatment adjustments were made based on imaging results indicating significant urological abnormalities. Symptom duration was recorded from onset to hospital admission. Defervescence, marking clinical recovery, was defined as a reduction in axillary temperature below 37°C. Therapy failure was recognized if symptoms persisted or worsened after five days of appropriate treatment, with relapse identified as symptom recurrence with the same microorganism within four weeks of antibiotic cessation, and reinfection ascribed to a different bacterial strain.

Data analysis in this study was performed using SPSS software (version 21.0), with statistical results reported as either medians and interquartile ranges (IQR) for continuous variables, or as frequencies and percentages for categorical variables. To assess differences between groups, t-tests were utilized for normally distributed continuous data, whereas the Mann-Whitney U test was applied to non-normally distributed data. For categorical data, the chi-square ($\chi 2$) test or Fisher exact test was used based on the data's suitability for these tests. The relationship between dichotomous variables was evaluated through odds ratios (OR) with 95% confidence intervals (CI). A p-value of less than 0.05 was considered statistically significant for all tests. In the preliminary analysis, variables associated with the outcome of interest at a p-value < 0.1 were identified and subsequently included in a multivariate logistic regression analysis, which was conducted using a backward selection process to identify factors independently associated with the outcome.

RESULTS

Within the cohort of 438 participants enrolled in this investigation, a distribution of 54.6% males (n=239) and 45.4% females (n=199) was observed. The median age of the participants was 48 years. A significant majority (n=413; 94.3%), were admitted either to the Internal Medicine or Urology departments, whereas a smaller proportion, (25; 5.7%), needed care in the Intensive Care Unit. For 282 (64.4%) of these patients, this incident represented their initial occurrence of complicated pyelonephritis, whereas the remaining 156 (35.6%) had documented previous episodes. The study noted that a substantial number of the episodes,(325; 74.2%), transpired in individuals presenting with structural or functional abnormalities within the genitourinary system. Additionally, a history of recurrent lower urinary tract infections (UTIs) was present in 115(26.3%) of the patients, and 193 (44.1)% had comorbid conditions, which included diabetes mellitus (115; 26.3%), hypertension (50; 25.91%), and chronic kidney disease (14.51%).

Table 1 delineates the criteria utilized to classify the incidence of complicated pyelonephritis among the study participants.

Table-1: ***Factors associated with Complicated Pyelonephritis in the study cohort***

Factors	Patients				Overall	
	Male	%	Female	%	N	%
Benign prostatic hyperplasia	34	14.23	0	0.00	34	7.76
Renal Stone	38	15.90	28	14.07	66	15.07
Structural bladder pathology	31	12.97	43	21.61	74	16.89
Neurogenic bladder	9	3.77	18	9.05	27	6.16
Ureteral or Urethral Obstruction due to causes other than stones	21	8.79	18	9.05	39	8.90
Ureter catheter or stent	9	3.77	3	1.51	12	2.74
Long-term bladder catheterization	36	15.06	33	16.58	69	15.75
Nephrostomy tube	11	4.60	9	4.52	20	4.57

Table-1: ***Factors associated with Complicated Pyelonephritis in the study cohort***

Factors	Patients				Overall	
	Male	%	Female	%	N	%
Immunocompromised	33	13.81	35	17.59	68	15.53
Anatomical or functional single kidney	17	7.11	12	6.03	29	6.62
Total	239	100.00	199	100.00	438	100.00

Prior to hospitalization, the median symptom presented with fevers exceeding 39°C, accompanied duration was observed to be three days, with an by flank pain in (273; 62.3%) of cases and interquartile range (IQR) from three to nine days. A costovertebral angle tenderness in 244 (55.71%) significant majority of the patient cohort (346; 79%). (Table-2_. Serum C-reactive protein (CRP) levels were assessed for 425 patients, among which 383 (90.12%) exhibited elevated levels, with a mean CRP concentration of 118 mg/L.

Table-2: ***Clinical Microbiological and Laboratory Data of study participants***

Clinical Data	N	%
Fever > 39 C	346	79.00
Flank pain	273	62.33
Chills	299	68.26
Systolic blood pressure < 90 mm Hg	44	10.05
Costovertebral tenderness	244	55.71
Pathogens isolated in our study population		
Escherichia coli	173	68.65
Proteus spp	30	6.85
Klebsiella spp	17	3.88
Enterobacter spp	12	2.74
Other Gram-positive bacilli	6	1.37
Enterococcus faecalis	4	0.91
Candida spp	2	0.46
Polymicrobial	7	1.60
Others	1	0.23
Laboratory Data		
C-reactive protein 26 mg/L (out of 425 patients)	383	90.12
Bacteriuria	127	29.00
Leukocytosis	328	74.89
Pyuria	357	81.51
Microscopic hematuria	162	36.99

Table-2: ***Clinical Microbiological and Laboratory Data of study participants***

Clinical Data	N	%
Thrombocytopenia	62	14.16

During the week prior to hospitalization, 41.1% (80 the presence of uropathogens in blood but not in individuals) of the study population had taken some urine cultures in 76.47%. form of antimicrobial treatment. Cultures of urine The pathogen profile in complicated pyelonephritis and blood were conducted for 365 and 239 patients, cases primarily featured Escherichia coli, respectively, revealing positive urine cultures in responsible for 68.65% (173 cases) of infections. 69% (252 individuals) and significant bacteremia in Proteus spp., and Klebsiella spp. were identified in 34.31% (82 individuals). Among the 228 patients 6.85% (30 cases) and 3.88% (17 cases), who underwent both tests, 14.91% (34 individuals) respectively. Other pathogens included exhibited discordant results. Of these, discrepancies Enterobacter spp. (2.74%, 12 cases), various Gramwere due to different isolates in 23.53% of cases and positive bacilli (1.37%, 6 cases), Enterococcus faecalis (0.91%, 4 cases), Candida spp. (0.46%, 2 cases), with polymicrobial sources in 1.60% (7 cases) and rare pathogens in 0.23% (1 case) of cases.

Diagnostic imaging was extensively utilized, with abdominal ultrasonography conducted on 79.91% (350 patients) within 48 hours of admission, identifying abnormalities in 60.86% (213 cases). Computed tomography (CT) scans were performed on 92 patients within five days of admission, detecting abnormalities in 73.91% (68 cases).

Ultrasound evaluations revealed ectasia grade II in 21.60% (46 cases), kidney or ureteral stones in 32.39% (69 cases), and complicated kidney cysts in 23.00% (49 cases). Kidney or perinephric abscesses and focal nephritis were identified in 13.15% (28 cases) and 9.86% (21 cases), respectively. CT imaging findings were consistent, with ectasia grade II in 60.29% (41 instances), stones in 8.82% (6 patients), and abscesses in 10.29% (7 patients), among others. Notably, 54.3% (19 out of 35) of abscesses diagnosed were larger than 3 cm in diameter, necessitating ultrasound- or CT-guided drainage.

Table-3 ***Findings on Ultrasonography and CT Abdomen***

	Ultrasound Abdomen (n=350; 79.9%)		CT Abdomen with / without contrast (n=92; 21%)	
	Number	%	Number	%
Clinically relevant findings on examination	213	60.86	68	73.91
Ectasia 2 grade II	46	21.60	41	60.29
Kidney or ureteral stones	69	32.39	6	8.82
Complicated kidney cysts	49	23.00	8	11.76
Kidney or perinephric abscess	28	13.15	7	10.29
Focal nephritis	21	9.86	6	8.82

In the initial management of empirical therapy, a combination of treatments was employed in 31.8% of cases, whereas single-agent therapies were used in 68.2% of instances. The effectiveness of these treatment approaches reached 92.4% upon identification of the causative pathogen. The study observed a 5.7% incidence of severe sepsis among the patients. The median duration to achieve apyrexia was reported as three days, and the average hospital stay was eight days. The mortality rate within the hospital setting stood at 6.89%, with 4.34% of these deaths being directly related to the acute health event. Post-discharge, 16.89% of patients were lost to follow-up. Of those who were followed, 89.01% were reported to have recovered, 7.42% experienced a relapse, and 3.57% were reinfected.

Univariate analysis identified several predictors significantly associated with mortality due to the health condition, including age above 60, severe sepsis, chronic kidney disease (CKD), acute renal failure (ARF) , immunocompromised status, absence of fever or costovertebral angle tenderness, elevated peripheral white cell count, systolic blood pressure below 90 mm Hg, creatinine levels above 2 mg/dL, thrombocytopenia, bacteremia, and septic shock. However, multivariate analysis revealed that advanced age (over 60 years), septic shock, and immunosuppression independently increased the risk of mortality, as detailed in Table 4 of the study.

Table 4 ***Association of various risk factors with attributable mortality in our study participants***

	Univariate Analysis (OR (95% Cl))	p	Multivariate Analysis (OR (95% Cl))
Age > 60 years	1.23 (0.89-2.23)	0.001	3.22 (1.83-4.93)
Ectasia ≥ grade II	2.01 (1.23_3.87)	0.06	
Absence of fever	1.24 (0.92-2.12)	0.002	
Long-term bladder catheterization	1.86 (1.01-3.23)	0.09	
Chronic kidney failure	1.97 (1.09-3.63)	0.02	
Acute kidney failure	6.29 (3.92-12.89)	0.002	
Serum creatinine > 2 mg /dL	2.12 (1.01-3.32)	0.004	
Leukocytosis > 20.000 cell/ml	1.21 (1.12-2.19)	0.02	
Systolic blood pressure <90 mm Hg	2.89 (1.34-5.78)	0.001	
Bacteremia	1.87 (1.11- 3.98)	0.008	
Thrombocytopenia	3.23 (1.48-4.98)	0.006	
Absence of costovertebral tenderness	1.10 (1.05-1.98)	0.03	
Severe sepsis	19.28 (5.45-28.43)	0.002	
Immunosuppression	1.92 (1.23-4.87)	0.001	2.87 (2.47-7.28)
Septic shock	48.23 (21.2-108.45)	0.02	62.3 (31.2-112.6)

DISCUSSION

The prevalence of complicated pyelonephritis, acquired from various sources such as community, healthcare settings, or hospitals, remains significant.[10,11] Research often categorizes complicated pyelonephritis within a broader spectrum of UTIs and acute pyelonephritis, leading to a heterogeneity that complicates clear analysis.[12,13] Our findings indicate a higher incidence of complicated pyelonephritis in males, with each case in this demographic being classified as complicated, aligning with the notion that pyelonephritis in males is inherently complex.[14–16] The median time to hospital admission post-symptom onset was noted at 2.5 days, consistent with recent studies.[17] The urine culture

positivity rate was found to be 69%, slightly lower than that associated with uncomplicated cases but in line with data on complicated pyelonephritis.[18–20] The discrepancy between urine and blood culture results in uncomplicated pyelonephritis is usually minor (2-3%), suggesting urine cultures could suffice for diagnosis.[23,24] However, complicated cases show a larger gap, with our study revealing a 14.91% discordance, primarily due to bacteremia in patients with negative urine cultures, corroborating prior research.[25] Notably, 41.1% of patients had received antibiotics before hospitalization, a practice that might reduce urine culture sensitivity.[25] In the context of urinary tract infections (UTIs), Escherichia coli remains the dominant pathogen. Yet, in complicated pyelonephritis, its prevalence does not exceed 65-70%, with our study observing a 68.65% detection rate. The significance of other gram-negative bacilli, including fermenting species like Klebsiella spp. and Proteus spp., and nonfermenters such as Pseudomonas aeruginosa and Acinetobacter baumanii, is underscored. An important study identified E. coli in 63% and Klebsiella spp. in 7% of 800 patients with complex UTIs, primarily complicated pyelonephritis.[25] Our study also noted that 13.97% of isolates were extended-spectrum β-lactamase (ESBL) producers, slightly above previously mentioned rates.[26,27] This diversity and the rise in ESBL-producing and multidrug-resistant organisms underline the importance of precise diagnostic approaches for the etiology of complicated pyelonephritis.

Within the context of acute pyelonephritis management, the utility of ultrasonography has been a subject of debate. Literature suggests its relevance is minimal in cases where patients show satisfactory progress following appropriate treatment, leading several scholars to question its necessity in such scenarios.[28,29] However, the application of ultrasonography in the initial evaluation of complex cases of pyelonephritis remains under-explored, contributing to the absence of widespread agreement on its use. In the present research, ultrasonography was conducted for 79.9% of patients upon their arrival at the hospital or within the first 48 hours of admission. This approach enabled the identification of clinically significant urological anomalies in 60.86% of these cases. Considering the substantial morbidity and the frequent discovery of conditions necessitating urgent medical intervention, this study advocates for the routine implementation of ultrasonographic evaluation in patients diagnosed with complicated pyelonephritis.

Furthermore, our findings reveal a 5.7% incidence of severe sepsis among the cohort, a rate lower than that reported in prior studies focusing exclusively on patients with complicated pyelonephritis.[9,17] The incidence of septic shock could potentially be higher, especially in individuals suffering from obstructive uropathy, with estimates reaching up to 21%.[30] This severity underscores the necessity for a significant proportion of patients to be admitted to Intensive Care Units (ICUs), as was the case for 5.7% of participants in this investigation.

The observed mortality rate linked to complex cases of pyelonephritis falls within a reported range of 3.2% to 9.8%, according to existing literature.[29,31,32] The present study found a crude mortality rate of 6.89% and an attributable mortality rate of 4.34%, aligning closely with findings by Buonaiuto et al.[29] This variance holds significant implications, highlighting the influence of underlying comorbid conditions in patients with complicated pyelonephritis on mortality outcomes.

Given the descriptive cross-sectional nature and the single-center design of this study, several limitations merit consideration. First, the findings are derived from a single tertiary care center, which may limit the generalizability of the results to other settings with different patient populations, healthcare practices, or resource availability. Second, the crosssectional design provides a snapshot of complicated pyelonephritis cases at a specific point in time but cannot establish causality or track changes over time. Third, the study's reliance on inpatient data may introduce selection bias, as it excludes patients with complicated pyelonephritis managed in outpatient settings or those who did not seek medical care. Fourth, despite rigorous diagnostic criteria, the potential for diagnostic bias exists, given the variability in clinical presentation and the interpretation of diagnostic tests. Additionally, the study may not have captured all relevant patient characteristics or comorbidities, which could influence outcomes or the generalizability of the findings. Finally, the study's observational nature limits the ability to control confounding factors that could influence the

results.

Conclusion

This study provides valuable insights into the clinical, epidemiological, and microbiological characteristics of complicated pyelonephritis in a tertiary care setting, along with outcomes associated with this condition. Despite its limitations, the findings underscore the importance of early diagnosis, comprehensive management, and consideration of underlying comorbidities in patients with complicated pyelonephritis. The study highlights the necessity of considering both antimicrobial resistance patterns and the potential impact of urinary tract abnormalities on treatment outcomes. Future research should focus on multicenter studies to enhance the generalizability of findings, longitudinal studies to better understand the progression of complicated pyelonephritis, and randomized controlled trials to evaluate the efficacy of different management strategies. Moreover, addressing the identified limitations could further refine our understanding of complicated pyelonephritis, contributing to improved patient care and outcomes.

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